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Comparative Clinical Pharmacology of Rocuronium, Cisatracurium, and Their Combination

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Background: **The comparative clinical pharmacology of cisatracurium and rocuronium and their combinations has not been reported. In this study, the authors compared the relative potency and the clinical profile and characterized the interaction of both drugs.**

Methods: **Two hundred twenty adults classified as American Society of Anesthesiologists physical status I and anesthetized with propofol–fentanyl–nitrous oxide were studied. In part 1, the neuromuscular-blocking effects of cisatracurium and rocuronium were assessed after administration of bolus doses of 20–50 μg/kg and 100–300 μg/kg, respectively. In part 2, we compared the time course of 1×ED_{50}, 1, 1.5, and 2×ED_{95} doses of both drugs (where ED_{50} and ED_{95} are, respectively, the doses producing 50% and 95% depression of the first twitch height [T1]). In part 3, equieffective combinations of both drugs were studied to characterize their interaction.**

Results: **The calculated ED_{50} values and their 95% confidence intervals were 111 (107–115) and 215 (207–226) μg/kg for rocuronium and cisatracurium, respectively. Compared with equipotent doses of cisatracurium, rocuronium had a faster onset, and a faster spontaneous T1 and train-of-four recovery times that were significant except at maximum recovery with the 2×ED_{95} dose. The interaction between rocuronium and cisatracurium was synergistic, and the time profile of the combination group was different from that of the single-dose groups.**

Conclusions: **Cisatracurium is four to five times more potent than rocuronium. Rocuronium had a faster onset of action, a shorter clinical duration, and a faster spontaneous recovery rate compared with equipotent doses of cisatracurium. (Key words: Dose response; isobolographic analysis; pharmacodynamics.)**

CISATRACURIUM (1R-Cis, 1′ R-Cis) is approximately four or five times more potent than atracurium (based on their respective ED_{95} values, the dose that produces 95% depression of the first twitch height) and has a similar neuromuscular-blocking profile to atracurium except for a slower onset.[1] Rocuronium, an aminosteroid compound, offers the fastest onset time of all currently available nondepolarizing neuromuscular-blocking agents.[2] Both rocuronium and cisatracurium are characterized by an intermediate duration of action.[1,2] To date, no data on the comparative pharmacologic properties of both drugs and their combinations have been reported. Naguib[3–6] and others[7] have shown that combinations of structurally similar neuromuscular-blocking drugs produce an additive response in humans and combinations of structurally dissimilar neuromuscular-blocking drugs resulted in a potentiating effect.

This three-part study was undertaken (1) to compare the potency of cisatracurium and rocuronium, (2) to characterize the interaction of both drugs by isobolographic analysis, and (3) to compare the neuromuscular-blocking effects of different equipotent doses of cisatracurium and rocuronium and their combinations in patients receiving nitrous oxide–opioid–propofol anesthesia.

Methods

After obtaining institutional approval and informed consent, we studied 220 patients of both sexes who were classified as American Society of Anesthesiolo-

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gists physical status I, had a mean age of 25.7 yr (SD, 6.4 yr), and weighed a mean of 66.8 kg (SD, 11.4 kg). All patients were undergoing elective procedures; had no neuromuscular, renal, or hepatic disease; and were not taking any drug known to interfere with neuromuscular function. All patients received 2 mg oral lorazepam 90 min before operation. An infusion of lactated Ringer's solution was started before induction of anesthesia in the arm contralateral to that used to monitor neuromuscular function. Standard monitoring was used, and the peripheral temperature was maintained at $> 32.5°C$.

Anesthesia was induced with 0.03 mg/kg midazolam, 2 to 2.5 mg/kg propofol, 4 or 5 μg/kg fentanyl, and 70% nitrous oxide in oxygen, and it was maintained with a continuous infusion of 50–140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol and nitrous oxide in oxygen (70:30 ratio) supplemented with incremental doses of fentanyl. After topical anesthesia with 4 ml 4% lidocaine, the trachea was intubated without the aid of a muscle relaxant. End-tidal concentrations of nitrous oxide, oxygen, and carbon dioxide were determined continuously using a multiple-gas analyzer (Capnomac, Datex Instrumentarium, Helsinki, Finland). Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide pressure, 36–40 mmHg).

The ulnar nerve was stimulated at the wrist with square wave supramaximal stimuli lasting 0.2 ms, delivered in a train-of-four (TOF) sequence and repeated every 12 s, using a Myotest peripheral nerve stimulator (Biometer International, Odense, Denmark). To facilitate stabilization of twitch height, we administered a 5-s, 50-Hz tetanus followed by a 2-min stabilization period.[8] The resultant contraction of the adductor pollicis muscle was recorded using a force displacement transducer and neuromuscular function analyzer (Myograph 2000, Biometer International). Approximately 200–300 g resting tension was applied to the thumb. The first twitch (T1) of the TOF was considered the twitch height. The amplitude of the first response (T1) in each TOF sequence was taken as the control to which all subsequent T1 values were compared.

The choice of drug and dose for any patient was made randomly. All patients received one dose of the neuromuscular blocker (or their combination). The time course of this dose was recorded and TOF measurements were continued until a TOF ratio had recovered spontaneously to 1.0 or had reached a maximum recovery for at least 10 consecutive stimuli.

Part 1: Dose–Response Studies

The following predetermined doses of drugs were administered: 100, 120, 150, 180, 240, or 300 μg/kg rocuronium and 20, 25, 30, 40, or 50 μg/kg cisatracurium. All drugs were administered to groups of 10 patients and were injected over 5 s into a rapidly flowing intravenous line. From the dose–response curves of rocuronium and cisatracurium, we determined the respective effective doses resulting in a 50% and 95% (ED_{50} and ED_{95}) reduction of the first twitch tension (T1). The neuromuscular response was recorded as the maximum depression of T1, expressed as a percentage of the control value. Data from patients in whom the injected dose of the neuromuscular blocker caused 1–99% block were used to calculate the dose response.

The percentage values for T1 depression in each group were transformed to probits and plotted against the logarithm of the dose using PCNONLIN version 4.2A (ClinTrials, Lexington, KY).[9] Regression lines were compared using analysis of covariance[10] and the BMDP statistical package (release 7.01, University of California Press, Berkeley, CA). The ED_{50} and ED_{95} values were calculated from the log-probit regression lines for each group.

Part 2: Clinical Studies

We investigated the time course of rocuronium- or cisatracurium-induced neuromuscular block in eight groups of patients ($n = 10$ in each) and compared equipotent doses of both drugs ($1 \times ED_{50}$, $1 \times ED_{95}$, $1.5 \times ED_{95}$, and $2 \times ED_{95}$).

Part 3: Interaction (Isobolographic) Studies

In part 3, the dose–response curves for a combination of the two drugs were obtained by administering the following drug combinations in a constant dose ratio based on the ED_{50} values of the single agent: (0.25 ED_{50} rocuronium + 0.25 ED_{50} cisatracurium; 0.5 ED_{50} rocuronium + 0.5 ED_{50} cisatracurium; and 0.75 ED_{50} rocuronium + 0.75 ED_{50} cisatracurium). The neuromuscular response was recorded as the maximum depression of T1, expressed as a percentage of the control value. In these studies, cisatracurium was administered first, followed 3 min later by rocuronium to ensure that the peak effect of both drugs coincided.

From the dose–response curve of the combined drugs, the ED_{50} value of the total dose of the mixture was calculated, and based on the known dose ratio, the single doses of the agents in the combination were obtained for plotting on the isobologram.[11,12]

The isobologram was constructed by plotting single-drug ED_{50} points on the dose coordinates of the isobologram and a combined ED_{50} point in the dose field. A straight line joining the single-drug ED_{50} points is called the "additive line." Confidence intervals (CIs) for each point were calculated from the variances of each component alone. The confidence intervals were evaluated for statistical significance using a Student's *t* test.

The algebraic (fractional) analysis[13] was used to describe the magnitude of the interaction. It was based on the expression of the component doses of the two agents of the combination as fractions of the doses that produce the same effect when given separately. The sum of the fractional doses, as expressed by the following equation, indicates the type of interaction:

$$dr/(ED_{50})_r + dc/(ED_{50})_C$$

Where $(ED_{50})_r$ and $(ED_{50})_C$ are, respectively, the ED_{50} values of rocuronium and cisatracurium given alone, and *d*r and *d*c are, respectively, the doses of rocuronium and cisatracurium that, when combined, are equipotent with $(ED_{50})_r$ or $(ED_{50})_C$. Values near 1 indicate additive interactions; values > 1 imply an antagonistic interaction; and values < 1 indicate a synergistic interaction.

Data Collected

The following variables were determined for all patients: time to first depression of T1 (lag time); maximum depression of T1 and TOF; time between administration of the neuromuscular blocker and maximum depression of T1 and TOF (onset time); times from injection to 25% (clinical duration), 75%, and 100% of control recovery of twitch tension, and times from injection to 0.25, 0.75, and 1 (or maximum) recovery of TOF ratio.

Data Analysis

Onset and recovery times were compared with a one-way analysis of variance and the Student-Newman-Keuls multiple-range test. In clinical studies, onset and recovery times of $1\times ED_{50}$ doses of rocuronium and cisatracurium were compared using the unpaired *t* test. Similar analyses were performed for $1\times ED_{95}$, $1.5\times ED_{95}$, and $2\times ED_{95}$ doses of both drugs. These analyses were done using the BMDP statistical package (release 7.01, University of California Press). Results were expressed as mean and SD or as 95% confidence intervals, and they were considered significant when $P < 0.05$.

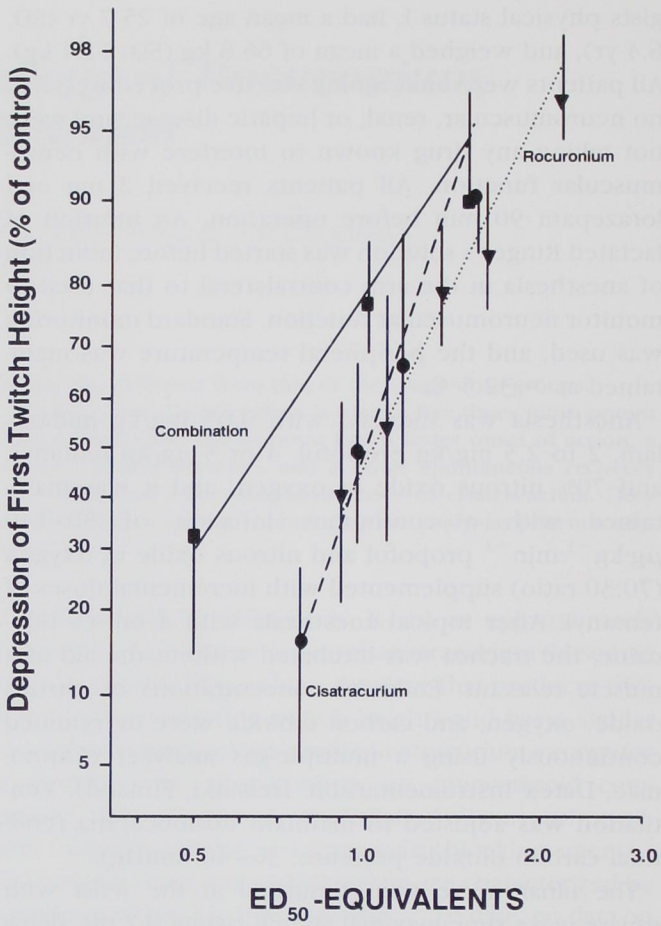

Fig. 1. Dose–response relations for the first twitch depression for rocuronium (▼. . .▼), cisatracurium (●- -●), and their combination (■–■). Individual points represent mean T1 depression (percent of control) with each dose, and the bars represent 95% CIs. Drug doses are represented as ED_{50} equivalents (the dose that produces 50% depression of the first twitch height).

Results

Dose-Response and Interaction Studies

The highest doses, 300 μg/kg rocuronium and 50 μg/kg cisatracurium, produced 100% depression of T1 in most of the patients, and these doses were excluded from the dose-response calculations. The slopes for the rocuronium-cisatracurium combination, rocuronium, and cisatracurium groups were 4.23, 5.91, and 8.75, respectively (fig. 1). The slopes of dose-response curves differed significantly. The calculated ED_{50} and ED_{95} values and their 95% confidence intervals for the rocuronium group were 111 (107–115) μg/kg and 215 (207–226) μg/kg, respectively. Corresponding values for the cisatracurium group were 26.2 (25.8–26.5) μg/kg and 39.8 (38.7–40.9) μg/kg, respectively.

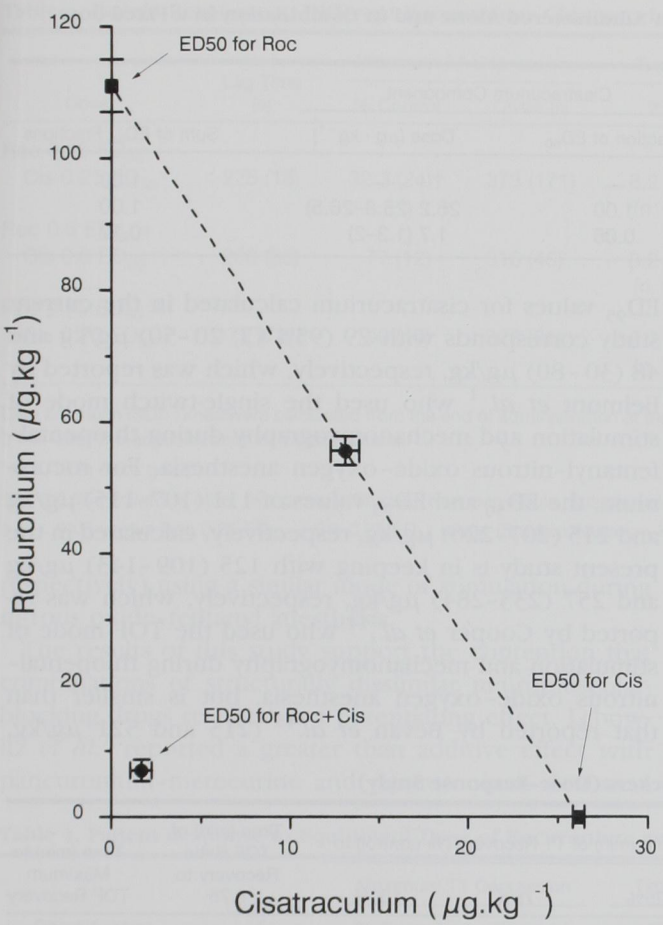

Fig. 2. The first-twitch ED_{50} (the dose that produces 50% depression of the first twitch height) isobologram for the interaction of rocuronium and cisatracurium. The dashed line connecting the single drug ED_{50} points is the theoretical additive line, and the point on this line is the theoretical additive ED_{50} point (95% CI). The experimentally determined ED_{50} dose (95% CI) of the rocuronium–cisatracurium combination fell significantly ($P < 0.0001$) below the corresponding theoretical additive point, indicating synergistic interaction.

The isobolographic analysis demonstrated a synergistic interaction with respect to the neuromuscular-blocking activity of the rocuronium and cisatracurium combination (fig. 2). The experimentally determined ED_{50} (and 95% CI) for the combination was 7.1 (5.4–8.7) μg/kg for rocuronium and 1.7 (1.3–2) μg/kg for cisatracurium. The theoretical additive ED_{50} (and 95% CI) was calculated to be 55.5 (53.3–57.7) μg/kg for rocuronium and 13.1 (12.6–13.6) μg/kg for cisatracurium. The confidence intervals of these points do not overlap, and the results of a Student's *t* test for the potency ratio were significant ($P < 0.0001$), indicating synergism. The fractional (algebraic) analysis of this interaction also demonstrated synergism (table 1).

Data describing onset and the spontaneous recovery are presented in tables 2 and 3. Increasing the dose of rocuronium or cisatracurium resulted in shorter mean times to onset of maximum neuromuscular block. Recovery times varied inversely with the dose administered. In the combination groups, doubling the dose resulted in potentiation of block by approximately 240% and prolongation of time to 100% T1 recovery by 130% and time to maximum TOF recovery by 165% (table 3).

Onset and Spontaneous Recovery Characteristics of Equipotent Doses

Compared with cisatracurium, equipotent doses of rocuronium (table 4) resulted in significantly shorter lag and onset times. For instance, onset times at $1\times ED_{50}$ and $2\times ED_{95}$ doses were, respectively, 180 s and 67 s faster with rocuronium than those observed with cisatracurium ($P = 0.0001$). Mean T1 recovery times to 25%, 75%, and 100% of control tension were 5.2–10.3 min faster after $1\times ED_{50}$ to $2\times ED_{95}$ doses of rocuronium compared with equipotent doses of cisatracurium (table 4). These differences were statistically significant except at a 100% recovery time with the $2\times ED_{95}$ dose. When plotted graphically, they appear as parallel recovery patterns (fig. 3A).

Similarly, the mean TOF ratio recovery time to 0.75 was significantly faster after $1\times ED_{50}$ to $2\times ED_{95}$ doses of rocuronium compared with equipotent doses of cisatracurium (table 4). When plotted graphically, they appear as parallel recovery patterns (fig. 3B).

Patient responses to $1\times ED_{50}$ dose of rocuronium, cisatracurium, or their combination are summarized in table 5. T1 and TOF recovery times in the combination group were noted to be either similar or longer than that observed with rocuronium, but they were significantly shorter compared with those of cisatracurium.

Discussion

Dose–Response and Interaction Studies

In this study, the calculated ED_{50} and ED_{95} values and their 95% confidence intervals were 26.2 (25.8–26.5) and 39.8 (38.7–40.9) μg/kg for cisatracurium group, respectively, rendering it approximately four or five times more potent than rocuronium (based on the estimate of ED_{50} or ED_{95}) in patients receiving nitrous oxide–opioid–propofol anesthesia. Corresponding values for the rocuronium group were 111 (107–115) μg/kg and 215 (207–226) μg/kg, respectively. In addition,

Table 1. ED_{50} Values and 95% CI for Rocuronium and Cisatracurium Administered Alone and in Combination in a Fixed-dose Ratio

	Rocuronium Component		Cisatracurium Component		
Group	Fraction of ED_{50}	Dose ($\mu g \cdot kg^{-1}$)	Fraction of ED_{50}	Dose ($\mu g \cdot kg^{-1}$)	Sum of ED_{50} Fractions
Rocuronium	1.00	111 (107–115)	—	—	1.00
Cisatracurium	—	—	1.00	26.2 (25.8–26.5)	1.00
Combination	0.06	7.1 (5.4–8.7)	0.06	1.7 (1.3–2)	0.12

isobolographic analysis (fig. 2) showed that combinations of rocuronium and cisatracurium were synergistic. The magnitude of this interaction can be appreciated by the examination of the fractional dose scores (table 1). The measured ED_{50} of the mixture was only 12% of the predicted value assuming a purely additive interaction.

It is well established that the frequency of stimulation can affect the evoked response. Therefore, the mode of stimulation used in this study (TOF) could result in an apparently greater potency of neuromuscular blockers compared with the single-twitch mode.[14] Because the same pattern of stimulation was used for all patients, the relative potencies of rocuronium and cisatracurium determined in this study are valid. In fact, the ED_{50} and ED_{95} values for cisatracurium calculated in the current study corresponds with 29 (95% CI, 20–50) μg/kg and 48 (30–80) μg/kg, respectively, which was reported by Belmont *et al.*,[1] who used the single-twitch mode of stimulation and mechanomyography during thiopental–fentanyl–nitrous oxide–oxygen anesthesia. For rocuronium, the ED_{50} and ED_{95} values of 111 (107–115) μg/kg and 215 (207–226) μg/kg, respectively, calculated in the present study is in keeping with 125 (109–143) μg/kg and 257 (233–284) μg/kg, respectively, which was reported by Cooper *et al.*,[14] who used the TOF mode of stimulation and mechanomyography during thiopental–nitrous oxide–oxygen anesthesia, but is smaller than that reported by Bevan *et al.*[15] (215 and 521 μg/kg,

Table 2. Patient Response to Different Doses of Neuromuscular Blockers (Dose–Response Study)

			Maximum T1 Depression		Time (min) of T1 Recovery (% control) to			Time (min) of TOF Ratio Recovery to 0.75	Time (min) to Maximum TOF Recovery
Dose* (μg/kg)	Lag Time (s)	ED_{50} Multiple	% Control	Onset (s)	25%	75%	100%		
Rocuronium									
100	40 (16)	0.9	40 (27)	197 (54)	—	8.0 (2.2) (n = 7)	9.8 (3.9)	10.6 (3.5) (n = 9)	17.7 (4.6)
120	30 (9)	1.08	55 (33)	183 (60)	4.5 (1.2) (n = 4)	8.2 (2.3) (n = 8)	10.4 (3.4)	11.5 (2.9) (n = 10)	18.6 (4.7)
150	25 (6)	1.35	79 (12)	198 (92)	6.1 (2.8) (n = 6)	12.3 (2.7) (n = 10)	18.5 (4.2)	16.3 (3.4) (n = 10)	27.1 (5.4)
180	29 (6)	1.62	84 (11)	191 (60)	7.6 (2.8) (n = 8)	13.8 (2.2) (n = 10)	18.1 (2.2)	19.8 (3.6) (n = 10)	32.6 (11.1)
240	23 (6)	2.16	96 (3)	149 (61)	13.3 (5) (n = 10)	21.5 (6.3) (n = 10)	29 (10.5)	27.0 (8.8) (n = 10)	38.9 (10.8)
300	24 (6)	2.7	99 (3)	119 (65)	19.1 (5.8) (n = 10)	26.2 (5.9) (n = 10)	32.5 (8.0)	33.8 (8.5) (n = 10)	51.3 (14.4)
Cisatracurium									
20	184 (89)	0.77	16 (15)	480 (154)	—	12.9 (6.9) (n = 3)	15.5 (7.0)	16.9 (6.5) (n = 7)	26.4 (10.3)
25	119 (82)	0.96	49 (25)	474 (134)	10.2 (0.1) (n = 2)	16.1 (3.9) (n = 7)	19.5 (7.8)	21.7 (6.4) (n = 9)	33.8 (11.9)
30	91 (32)	1.15	66 (28)	439 (62)	12.3 (2.5) (n = 5)	18.5 (5.3) (n = 9)	25.6 (6.8)	27.4 (4.6) (n = 10)	42.9 (7.8)
40	78 (29)	1.54	90 (8)	420 (164)	18.5 (6.7) (n = 9)	27.8 (7.8) (n = 10)	32.9 (7.9)	35.3 (8.1) (n = 10)	50.7 (8.4)
50	64 (15)	1.92	98 (2)	290 (107)	24.1 (8.5) (n = 10)	32.2 (12) (n = 10)	39.7 (13.9)	41.6 (13) (n = 10)	52.8 (14.6)

Data are mean (SD). Times were calculated from the end of administration of the neuromuscular blocking drug.

* n = 10 in each group.

Table 3. Patient Response to Different Rocuronium–Cisatracurium Combinations (Interaction Study)

Dose*	Lag Time (s)	Maximum T1 Depression		Time (min) of T1 Recovery (% control) to			Time (min) of TOF Ratio Recovery to 0.75	Time (min) to Maximum TOF Recovery
		% Control	Onset (s)	25%	75%	100%		
Roc 0.25 ED_{50} + Cis 0.25 ED_{50}	225 (18)	32.3 (24)†	373 (171)	8.2 (0.2) (n = 2)	9.6 (6.2) (n = 5)	14.1 (5.2)	13.5 (6.9) (n = 7)	20.1 (7.3)†
Roc 0.5 ED_{50} + Cis 0.5 ED_{50}	200 (26)	77 (12)	310 (45)	8.2 (2.2) (n = 4)	14.1 (2.9) (n = 9)	18.4 (5.8)	19.3 (5.2) (n = 10)	32.8 (9.5)†
Roc 0.75 ED_{50} + Cis 0.75 ED_{50}	172 (72)‡	90 (10)	328 (81)	16.7 (4.2)† (n = 8)	22.9 (6.9)† (n = 10)	30.7 (10)†	29.8 (8.1)† (n = 10)	42.2 (10.5)†

Data are mean (SD). Times were calculated from the end of administration of the first neuromuscular blocking drug (cisatracurium). Rocuronium was administered 3 min after the administration of cisatracurium.

* n = 10 in each group.

† $P < 0.05$ *versus* the other two groups (Student-Newman-Keuls multiple range test).

‡ $P < 0.05$ *versus* Roc 0.25 ED_{50} + Cis 0.25 ED_{50} group (Student-Newman-Keuls multiple range test).

respectively) using a similar mode of stimulation during nitrous oxide–fentanyl anesthesia.

The results of this study support the contention that combinations of structurally dissimilar neuromuscular-blocking drugs resulted in a potentiating effect. Lebowitz *et al.*[7] reported a greater than additive effect with pancuronium–metocurine and pancuronium–d-tubocurarine combinations but not with a metocurine–d-tubocurarine combination. Similarly, Naguib[6] and Meretoja *et al.*[16] showed, respectively, that rocuronium–mivacurium and vecuronium–atracurium combinations produced synergistic effects. On the other hand, combinations of structurally similar neuromuscular-blocking drugs produce an additive response in humans.[3,4,6,7]

Table 4. Patient Response to Equipotent Dose of Rocuronium and Cisatracurium (Clinical Study)

Dose* (μg/kg)	Lag Time (s)	Maximum T1 Depression		Time (min) of T1 Recovery (% control) to			Time (min) of TOF Ratio Recovery to 0.75	Time (min) to Maximum TOF Recovery
		% Control	Onset (s)	25%	75%	100%		
Rocuronium								
111 (1 × ED_{50})	41 (17)†	50.1 (17)	204 (57)†	—	6.6 (3.7)‡ (n = 8)	11.4 (3.9)‡	10.9 (4.1)†	19.4 (4.9)†
216 (1 × ED_{95})	31 (11)†	94.3 (7)	193 (64)‡	9.9 (3.5)¶ (n = 10)	16.3 (3.5)¶ (n = 10)	19.3 (4.2)‡	21.1 (3.9)‡	32.2 (5.3)¶
324 (1.5 × ED_{95})	29 (8)†	99.6 (1)	116 (67)‡	16.9 (2.4)§ (n = 10)	24.9 (5.1)‡ (n = 10)	31.3 (9.2)¶	31.4 (5)§	49.6 (9.2)¶
432 (2 × ED_{95})	31 (3)‡	100 (0)	76 (19)†	24.4 (4.7)§ (n = 10)	32.7 (8.8)‡ (n = 10)	39.6 (13.1)	42.8 (10.9)¶	59.7 (12.5)
Cisatracurium								
26 (1 × ED_{50})	102 (36)	52.8 (20)	384 (76)	7.5 (2.3) (n = 4)	13.2 (3.2) (n = 9)	17.3 (4.7)	20.6 (3.9)	29.9 (3.6)
40 (1 × ED_{95})	77 (19)	94 (8)	346 (124)	15.1 (5.3) (n = 9)	22.3 (5.6) (n = 10)	27.1 (6.9)	29.9 (7.8)	43.4 (11.5)
60 (1.5 × ED_{95})	67 (16)	99.4 (1)	261 (129)	26.9 (7.1) (n = 10)	34.7 (7.2) (n = 10)	39.5 (7.7)	47.2 (9.3)	62.8 (14.7)
80 (2 × ED_{95})	45 (12)	99.8 (0.6)	143 (37)	34.7 (5.6) (n = 10)	42.8 (5.9) (n = 10)	47.4 (6.6)	53.6 (6.6)	68.2 (7.9)

Data are mean (SD). Times were calculated from the end of administration of the neuromuscular blocking drug.

* n = 10 in each group.

† $P \leq 0.0001$ (comparisons were made at the same ED value using unpaired *t* test).

‡ $P < 0.001$ (comparisons were made at the same ED value using unpaired *t* test).

§ $P < 0.01$ (comparisons were made at the same ED value using unpaired *t* test).

¶ $P < 0.05$ (comparisons were made at the same ED value using unpaired *t* test).

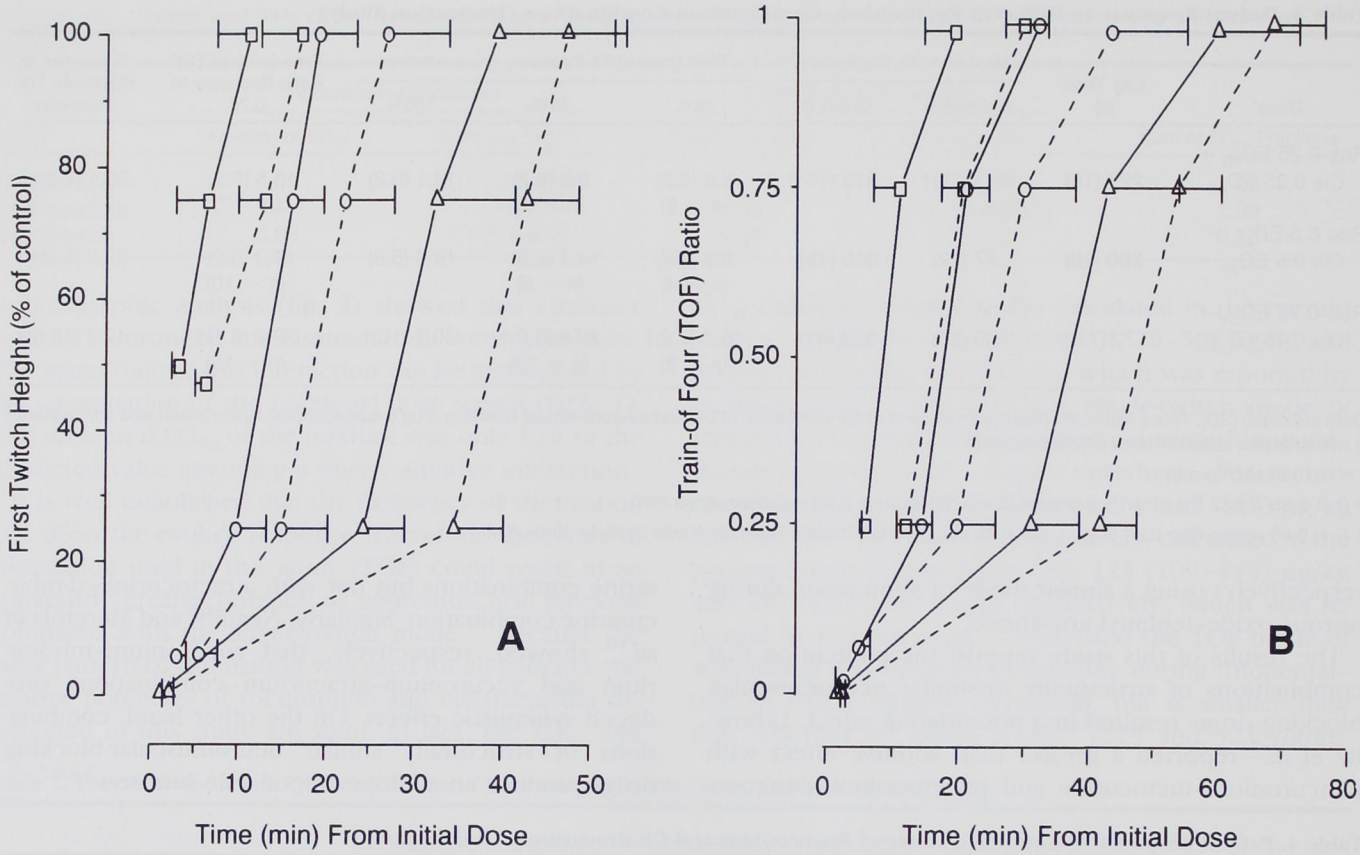

Fig. 3. Spontaneous recovery of the (*A*) T1 or (*B*) TOF ratio after administration of equipotent doses of rocuronium ($1\times ED_{50}$ = □–□, $1\times ED_{95}$ = ○–○, and $2\times ED_{95}$ = △–△) or cisatracurium ($1\times ED_{50}$ = □- -□, $1\times ED_{95}$ = ○- -○, and $2\times ED_{95}$ = △- -△). The mean T1 recovery times to 25%, 75%, and 100% of control tension were 5.2–10.3 min faster after $1\times ED_{50}$ to $2\times ED_{95}$ doses of rocuronium compared with equipotent doses of cisatracurium. The mean TOF recovery times to 0.25, 0.75, and maximum recovery were 5.4–13.2 min faster after $1\times ED_{50}$ to $2\times ED_{95}$ doses of rocuronium compared with equipotent doses of cisatracurium. These differences were statistically significant except at maximum recovery with the $2\times ED_{95}$ dose. ED_{50} and ED_{95} are the doses that produce 50% and 95% depression, respectively, of the first twitch height. Solid lines represent rocuronium, while broken lines represent cisatracurium.

Onset and Spontaneous Recovery Characteristics of Rocuronium and Cisatracurium

This study showed that rocuronium was associated with a significantly faster onset than cisatracurium. Rocuronium in doses twice the ED_{95} produced maximal block in 1.3 (0.3) min compared with 2.4 (0.6) min ($P < 0.0001$) with equipotent doses of cisatracurium. Another important observation was related to the recovery characteristics of the two drugs. Compared with cisatracurium, rocuronium had significantly shorter T1 and TOF spontaneous recovery times at $1\times ED_{50}$, $1\times ED_{95}$, and $1.5\times ED_{95}$ doses (table 4). At these doses, clinical duration and time to complete TOF recovery were noted to be, on average, 10 min longer with cisatracurium (table 4). Although at $2\times ED_{95}$ doses the differences in recovery times (8 or 9 min) were not statistically significant, it could be viewed as clinically important. The reason for this alteration in the recovery characteristics with $2\times ED_{95}$ doses is not apparent, but it could be attributed to changes in the pharmacokinetics of rocuronium at higher doses. For instance, Wright *et al.*[17] showed that the cumulative effects of both vecuronium and atracurium with increasing dose (within the clinical dose range) could be explained in part by a shift in recovery from the distribution phase to the elimination phase of the plasma concentration-*versus*-time curve. Further, unlike rocuronium, we found that the times to complete spontaneous recovery of T1 and the TOF ratio with subparalyzing doses ($1\times ED_{50}$) of the rocuronium–cisatracurium combination was significantly shorter than that observed with equipotent doses of cisatracurium (table 5).

Because cisatracurium is four or five times more potent than rocuronium (as shown in this study), it is not

Table 5. Patient Response to 1 × ED_{50} of Rocuronium, Cisatracurium, or Their Combinations

Drug*	Maximum T1 Depression (% control)	Time (min) of T1 Recovery (% control) to			Time (min) of TOF Ratio Recovery to 0.75	Time (min) to Maximum TOF Recovery
		25%	75%	100%		
Rocuronium	50.1 (17)	—	6.6 (3.7) (n = 8)	11.4 (3.9)	10.9 (4.1)	19.4 (4.9)
Cisatracurium	52.8 (20)	7.5 (2.3) (n = 4)	13.2 (3.2) (n = 9)	17.3 (4.7)	20.6 (3.9)†	29.9 (3.6)†
Combinations	32.3 (24)	8.2 (0.2) (n = 2)	9.6 (6.2)† (n = 5)	14.1 (5.2)†	13.5 (6.9) (n = 7)	20.1 (7.3)

Data are mean (SD). Times were calculated from the end of administration of the neuromuscular blocking drug or from the end of administration of the first neuromuscular blocking drug (cisatracurium) in the combination group. In the latter group, rocuronium was administered 3 min after the administration of cisatracurium.

* n = 10 in each group.

† $P < 0.05$ *versus* other groups (Student-Newman-Keuls multiple range test).

unexpected that its onset was slower than that of rocuronium (tables 2 and 4). Rocuronium offers the fastest onset time of all currently available nondepolarizing neuromuscular blockers,[2] and this has been attributed to its low potency,[18] different buffering mechanism (*i.e.*, the repetitive binding of relaxant molecules),[19] or both. Although fast onset of rocuronium cannot be satisfactorily explained by the difference in molar potency,[20] lower potency correlated with a faster onset of action.[21,22]

The onset time and maximum twitch suppression for cisatracurium and rocuronium reported in this study is consistent with other published studies.[1,14] Belmont *et al.*[1] noted that the mean onset time and mean percentage twitch suppression for 20, 30, 40, and 50 μg/kg cisatracurium were 7.4, 7.9, 7.7, and 7.6 min, and 13.2%, 70.7%, 80.7%, and 93%, respectively. Corresponding data reported in this study (table 2) were 8, 7.3, 7, and 4.8 min, and 16%, 66%, 90%, and 98%, respectively. With rocuronium, Cooper *et al.*[14] noted that the mean onset time and the mean percentage twitch suppression (using TOF stimulation) for 100, 150, and 300 μg/kg doses were 2.2, 2.8, and 1.7 min, and 28%, 76%, and 97%, respectively. Corresponding values in this study (table 2) were 3.3, 3.3, and 2 min and 40%, 79%, and 99%, respectively. Detailed spontaneous recovery characteristics of subparalyzing doses of rocuronium and cisatracurium have not been studied previously.

In figure 3, spontaneous T1 and TOF recovery appear as parallel recovery patterns. It has been shown that the clearance of two times the ED_{95} of cisatracurium was similar to that reported with equipotent doses of rocuronium (5.28 and 5.03 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively) in young adults free of hepatic or renal disease.[23,24]

In conclusion, this study shows that cisatracurium and rocuronium have different pharmacodynamic profiles. Based on the estimate of ED_{50}, the relative potency for rocuronium:cisatracurium was 1:4.2. As expected, the onset time to neuromuscular block after rocuronium was significantly shorter than after comparable doses of cisatracurium. Compared with cisatracurium, rocuronium had significantly shorter T1 and TOF spontaneous recovery times at $1 \times ED_{50}$, $1 \times ED_{95}$, and $1.5 \times ED_{95}$ doses. At these doses, clinical duration and time to complete TOF recovery were noted to be, on average, 10 min longer with cisatracurium. However, the differences in the maximum recovery times (8 or 9 min) noted at the $2 \times ED_{95}$ dose were not statistically significant. Isobolographic and algebraic analyses showed that the interaction of the rocuronium and cisatracurium combination is the result of a synergistic action at the neuromuscular junction. Comparison of the clinical profiles of equipotent doses ($1 \times ED_{50}$) of rocuronium, cisatracurium, or their combination revealed that the times to complete spontaneous recovery of T1 and the TOF ratio with the rocuronium–cisatracurium combination were significantly shorter than that observed with cisatracurium, but they were similar or longer than that of rocuronium.

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